

Review

The Function of Steroid Receptor Coactivator-1 in Normal Tissues and Cancer

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Received: 2012.01.19; Accepted: 2012.02.20; Published: 2012.03.07

Abstract

In 1995, the steroid receptor coactivator-1 (SRC-1) was identified as the first authentic steroid receptor coactivator. Since then, the SRC proteins have remained at the epicenter of coregulator biology, molecular endocrinology and endocrine-related cancer. Cumulative works on SRC-1 have shown that it is primarily a nuclear receptor coregulator and functions to construct highly specific enzymatic protein complexes which can execute efficient and successful transcriptional activation of designated target genes. The versatile nature of SRC-1 enables it to respond to steroid dependent and steroid independent stimulation, allowing it to bind across many families of transcription factors to orchestrate and regulate complex physiological reactions. This review highlights the multiple functions of SRC-1 in the development and maintenance of normal tissue functions as well as its major role in mediating hormone receptor responsiveness. Insights from genetically manipulated mouse models and clinical data suggest SRC-1 is significantly overexpressed in many cancers, in particular, cancers of the reproductive tissues. SRC-1 has been associated with cellular proliferation and tumor growth but its major tumorigenic contributions are promotion and execution of breast cancer metastasis and mediation of resistance to endocrine therapies. The ability of SRC-1 to coordinate multiple signaling pathways makes it an important player in tumor cells' escape of targeted therapy.

Key words: nuclear receptor; coactivator; SRC-1; transcription; development; cancer.

Introduction

Coregulator proteins were initially thought to be mere "acceptor proteins" that facilitated the interaction of specific ligand-bound nuclear receptors with general transcriptional machinery [1]. Over the last seventeen years, however, complex and essential roles for a cohort of over 350 coactivator proteins have steadily emerged [2]. Coregulator proteins have the uncanny ability to bind across unrelated families of transcription factors and coordinately facilitate the efficient and successful transcriptional activity of multiple target genes.

The nuclear receptors (NRs) comprise a large superfamily of proteins that bind as homo- or heterodimers to specific DNA elements in order to elicit transcriptional activation of target genes. Specifically, the steroid nuclear receptors or class I NRs are recruited to gene promoters upon the binding of a high-affinity ligand, which induce conformational changes in the NR essential for its activity. The significance of NR coregulator proteins came to light when *in vitro* experiments using purified NRs and basal transcription factors proved relatively incapable

of inducing transcriptional activation on their own [3, 4]. Furthermore, NRs were also shown to compete with each other for these essential coregulators as overexpression of one NR appeared to inhibit the transactivation function of another [5].

The steroid receptor coactivator 1 (SRC-1, also known as NCOA1) was first discovered in 1995 in a yeast two-hybrid screen based on its interaction with the ligand binding domain (LBD) of progesterone receptor (PR) [6]. This work represented the first cloning of an authentic NR coactivator. SRC-1 had the ability to interact with and coactivate NRs in the presence of hormones. These SRC-1 coregulated NRs include PR, glucocorticoid receptor (GR), estrogen receptor alpha (ER α), thyroid receptor (TR), retinoid X receptor (RXR), hepatocyte nuclear factor 4 (HNF4 α) and peroxisome proliferator-activated receptor γ (PPAR γ) [6-8]. The binding affinity of SRC-1 for these NRs has been shown to vary depending on where it specifically binds the NR. SRC-1 can bind NRs via its central region or less commonly via its C-terminal domain. The central domain of SRC-1 has been shown to be unable to bind to AR and only exhibits a poor binding affinity for GR. In contrast, the C-terminus of SRC-1 exhibits a poor binding affinity for ER, VDR, RAR and TR, relative to its central domain [9]. Furthermore, fluorescence resonance energy transfer (FRET) experiments have shown that the complex formed between ER α and SRC-1 exhibited a particularly high affinity binding, compared to other SRC-1/NR complexes [10]. Importantly, SRC-1 coactivator activity is not limited to the transcriptional co-activation of NRs, SRC-1 is also capable of coactivating other non steroidal transcription factors such as AP-1, serum response factor, NF κ B, Ets2, PEA3 and HOXC11 [11-17].

SRC-1 is the founding member of the p160 SRC family which also includes SRC-2 (NCOA2, TIF2 or GRIP1) and SRC-3 (AIB1, p/CIP, ACTR, RAC3 or NCOA3) [18, 19]. Each member is approximately 160 kDa in size and their sequences are largely conserved across family members and also across species. The p160 SRC family members also have overlapping coactivator functions and transfection assays have shown that all three can coactivate GR, PR and ER α [6]. The potential for functional redundancy among the three members may serve to ensure a safety mechanism in the regulation of numerous important biological processes that are associated with NR signaling.

Structural and Functional Domains of SRC-1

NR coactivators are unable to bind directly to the

DNA. Instead they form multiple contacts with the NR and with each other in multi-protein cooperative coactivator complexes. Initial investigations into coactivator complexes reported that steady-state SRC complexes consist of six to ten stably associated proteins and many more loosely-bound proteins [20]. The versatile structural domains of SRC-1 and the other SRC family members grant them a central position in such complexes, from which they regulate multiple biochemical processes critical for the successful execution of transcription.

1. The N-terminal domain

The SRC-1 protein structure is composed of several distinct functional domains. The N-terminus contains a basic helix-loop-helix-Per/Ah receptor nuclear translocation/Sim (bHLH/PAS) motif and is the most conserved region among the SRC family members with 75% similarity [4]. The bHLH/PAS domain is important for the protein-protein interactions that recruit secondary coactivators or co-coactivators to maximize the transcriptional activity of NRs (Figure 1). The domain is also important for the dimerization of SRC proteins and for the differential regulation of target genes [21, 22]. Nonetheless, cell-free chromatin transcription assays have shown that, although the bHLH/PAS domain can maximize the transcriptional potential of a complex, transcription can still occur in its absence. For instance, an N-terminal-deleted form of SRC-1 exhibits coactivation of PR-dependent transcription comparable to that of wild-type SRC-1 [23]. More recent studies have shown that the bHLH/PAS domain also has a bipartite nuclear localization signal (NLS) essential for the import and export of the SRC proteins between the nucleus and the cytoplasm. Mutation of two key residues Lys 17 (K17) and Arg 18 (R18) within this region of the bHLH/PAS domain prevented nuclear localization of all three p160 family members [24].

2. The nuclear receptor interaction domain (NRID)

The central region of the SRC-1 protein contains the nuclear receptor interaction domain (NRID). This domain contains three α -helical LXXLL (L, leucine; X, any amino acid) motifs which are essential for interaction of SRC-1 with its specific NRs (Figure 1) [25, 26]. These LXXLL motifs are the most common feature among the highly diverse group of coregulators [27]. Distinct LXXLL motifs along with their specific flanking sequences exhibit different binding affinities for different NRs inferring that NRs may prefer one LXXLL motif over another in the same coactivator or even prefer one coactivator over another [27, 28].

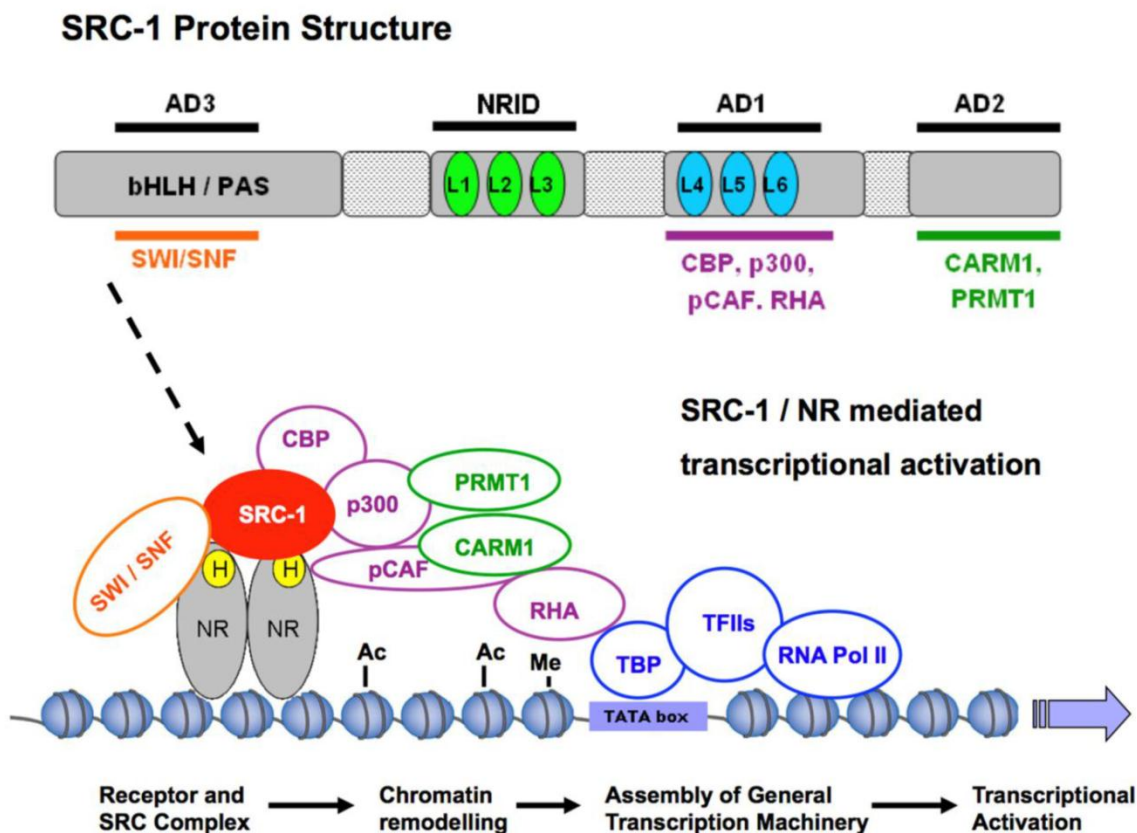


Figure 1. SRC-1-mediated coactivation of NRs. To exert its coactivation function in transcription, SRC-1 interacts with hormone (H)-bound nuclear receptors (NRs) to recruit other components of a large coactivator complex to the hormone response elements of a target gene. Specifically, SRC-1 binds NRs through one of its three LXXLL motifs (L1, L2 and L3) in the NR interaction domain (NRID) and interacts with CBP and p300 through its activation domain I (AD1), with CARM1 and PRMT1 through its AD2 and with SWI/SNF through its AD3. p/CAF is a p300/CBP-associated factor. CBP, p300 and p/CAF are histone acetyltransferases. CARM1 and PRMT1 are histone methyltransferases. RHA is a RNA helicase. SWI/SNF is an ATP-dependent chromatin remodeling complex. The formation of such a coactivator complex results in chromatin remodeling and bridges the hormone-activated NRs with the general transcription machinery for transcriptional activation of their specific target genes. bHLH/PAS: basic helix-loop-helix-Per/Ah receptor nuclear translocation/Sim motif; Ac: acetylation; Me: methylation; TBP, TATA-binding protein.

The LXXLL core motifs in SRC-1 have shown distinct preferences for steroid and retinoid receptors. In particular, a hydrophobic residue at position -1 relative to the first conserved leucine and a nonhydrophobic residue at position +2 have a strong impact on the affinity and selectivity of the coactivator motifs to bind to certain NR LBDs [29].

Secondary structural analysis of the central region shows that LXXLL motifs form an amphipathic α -helix which binds to a hydrophobic cleft that forms in the ligand-binding domains of NRs once ligands have bound [30]. Interactions between the leucine residues of the LXXLL motif and the hydrophobic cleft stabilize the SRC-1/NR complex [31]. Mutation of these leucine residues have been shown to inhibit the binding of SRC-1 to the ER α LBD *in vitro* and SRC-1-mediated activation of ER α *in vivo* [26].

3. The C-terminal domain

The C terminal domain of SRC-1 contains two intrinsic transactivation domains: AD1 and AD2. The AD1 domain is required for the recruitment of secondary coactivators, such as cAMP response element binding protein (CREB)-binding protein (CBP) and the histone acetyltransferase p300 (Figure 1). Once SRC-1 has complexed with its ligand-bound receptor at the DNA, it must bring in additional proteins such as CBP and p300 to acetylate histone residues within the enhancer and promoter regions of the target gene so that transcription can successfully occur. *In vitro* transcription assays from chromatin-assembled templates have demonstrated that the interaction of p300 with the AD1 domain of SRC-1 is essential for SRC-1-mediated coactivation of ER α [32]. Further-

more, observations from the p300 protein structure have confirmed that it is the SRC-1 interacting domain and not the ER α -interacting domain, that is essential for p300-mediated coactivation of ER α [32]. Additional experiments have demonstrated that the C terminus of SRC-1 and also SRC-3 have intrinsic histone acetyltransferase activity (HAT); however, it remains unclear if such HAT activity is significant for target gene activation as the SRC-1 intrinsic HAT activity is much weaker than that in the CBP/p300 proteins [33, 34]. SRC-1 also uses its AD1 domain to interact directly or indirectly via CBP/p300 with another HAT protein known as p/CAF (Figure 1). p/CAF primarily acetylates histone H3 and H4 to further facilitate chromatin remodeling at the site of NR target genes [35].

The AD1 domain is also responsible for interactions with the general transcription machinery [36, 37]. The AD1 has three LXXLL-like motifs and if any of these motifs are mutated there is a consequential disruption of SRC-1 interaction with the general transcription machinery [38, 39]. Additionally, RNA helicase A (RHA) may be recruited to the SRC-1-CBP/p300 complex at the AD1 domain and interacts with RNA polymerase II, bringing NRs into touch with the general transcription machinery (Figure 1) [40].

The AD2 domain of SRC-1 recruits histone methyl transferases (HMTs) such as coactivator-associated arginine methyltransferase 1 (CARM1) and protein arginine N-methyltransferase 1 (PRMT1) (Figure 1). CARM1 is a histone H3 specific arginine methyltransferase, which specifically methylates histone H3 at arginines 2, 17, and 26. CARM1 can only enhance NR transcription in the presence of a SRC protein and mutation of its binding domain will reduce its HMT activity and ability to act as a co-coactivator [41]. There appears to be a cooperative effort at play between the recruited co-coactivators as CBP-mediated acetylation of H3K18 has been shown to promote CARM1-mediated methylation of H3K17 [42]. CARM1 and PRMT1 can also act in synergy to enhance transcription [41]. PRMT1 acts on a different substrate to CARM1 and specifically methylates H4 at arginine 3 [43]. Again cooperative crosstalk is observed between PRMT1 and p300 as PRMT1-mediated H4 methylation at arginine 3 facilitates the subsequent acetylation of histone H4 tails by p300 [44].

Recently, a third activation domain (AD3) has been identified in the bHLH/PAS domain. This region also binds co-coactivators for NR mediated transcription. Many of these AD3 co-coactivators function synergistically with the other co-coactivators

that bind to the AD1 and AD2 domains of SRCs [45]. The co-coactivator BAF57, a subunit of the SWI/SNF ATP-dependent chromatin remodeling complex, binds to SRC-1 within its AD3 domain and potentiates SRC-mediated coactivation [46].

4. Post translational modification of SRC-1

SRC proteins are regulated by numerous post translational modifications (PTMs), which are crucial for determining protein stability, transcription factor interaction specificity and transcriptional activation [47]. In addition to ER, SRC-1 is regulated via alternative cellular signaling pathways which phosphorylate it at seven distinct sites *in vivo*. All of these phosphorylation sites contain a consensus sequence for proline-directed protein kinases. Phosphorylation of SRC-1 can also occur via Src kinase activity [48] and the mitogen-activated protein kinases (MAPK), ERK1 and ERK2 [49]. Growth factors such as EGF, interleukin-6 and cAMP can all induce phosphorylation of SRC-1 at specific consensus sites to increase its coactivator activity for ligand-bound and unliganded steroid receptor proteins. It has been shown that cAMP-induced phosphorylation of SRC-1 at Thr¹¹⁷⁹ and Ser¹¹⁸⁵ contribute to the steroid independent activation of both ER α and PR [50], whilst EGF-induced phosphorylation of SRC-1 can increase PR-dependent transcription [49].

SRC-3 has been previously associated with a specific PTM known as the glycogen synthase 3 (GSK3 β) phospho-ubiquitin clock [51]. Initially, this PTM was believed to be specific to SRC-3 however a recent study has shown that SRC-1 is subject to similar regulation [52]. The phospho-ubiquitin clock refers to the phosphorylation of the SRC protein by GSK3 β which increases the rate of turnover and the interaction of the SRC protein with a specific NR and then induces the ubiquitylation of the protein to ensure that the transcriptional event terminates at an appropriate time [53]. Current evidence suggests that the phospho-ubiquitin clock is conserved across all three p160 family members [52], this is an important mechanism through which the SRC proteins can maintain tight regulatory control over their many biological processes.

Biological Functions of SRC-1

1. The role of SRC-1 in reproduction and the uterus

Numerous studies over the years have accumulated evidence and shown that the SRC-1 protein is widely expressed in different tissues (Figure 2). SRC-1 knockout mice were generated to investigate the basic

biological functions of SRC-1 in these tissues [54]. The targeted deletion of the *SRC-1* gene in mice disrupted its nuclear receptor binding and transcriptional activation functions and presumably, its recruited HAT activity from the secondary coactivators such as CBP, p300 and p/CAF [54]. Despite these disruptions, SRC-1 null mice exhibited no obvious phenotype. Both male and female homozygotes were fertile and displayed a similar growth rate compared to the wild type mice [54]. However, further investigations revealed that steroid activity was partially impaired in SRC-1 null mice. Disruption of SRC-1 reduced estrogen-induced uterine growth; hence SRC-1 null mice achieved less than 60% uterine growth than that of the wild type mice when treated with estrogen. Furthermore, it was observed that SRC-1 is required for maximal uterine response to steroid hormones *in vivo* [54]. SRC-1 is required for estrogen and progesterone-induced activities of ER and PR in the uterus but not in the breast [55]. Furthermore, mitogen-inducible gene 6 (Mig6) has been identified as a downstream target of PR and SRC-1 in the uterus. Mig6 is required to maintain endometrial homeostasis in response to estrogen and has also been proposed as an important protein in the suppression of endometrial cancer [56].

SRC-1 is also expressed in the glandular and stromal cells of the normal endometrium. Immunoprecipitation assays revealed that estrogen-induced SRC-1 interaction with endometrial ER α only occurred during the proliferative phase of the menstrual cycle, indicating that SRC-1 has a regulatory role specific to this cycle phase [57, 58].

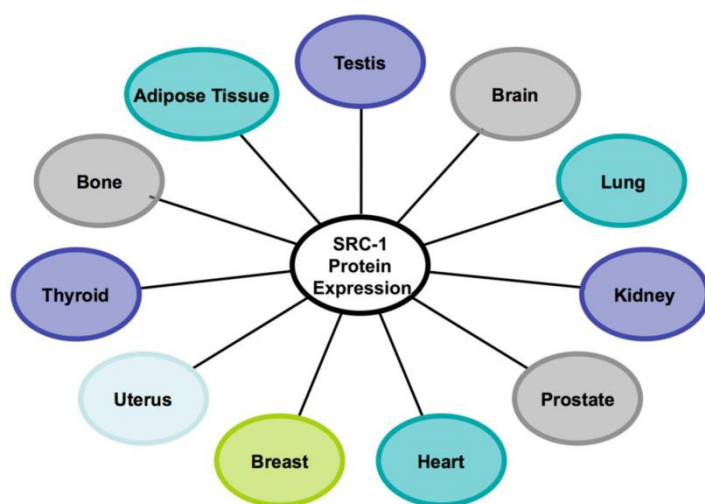


Figure 2. The human tissues with SRC-1 protein expression.

2. The role of SRC-1 in the prostate and testis

SRC-1 is also a known coactivator of the androgen receptor (AR) and it is recruited alongside SWI3-related gene product (SRG3) for AR-mediated cell proliferation during prostate development and regeneration [59]. SRC-1 null male mice exhibit reduced responsiveness to androgen stimulation versus controls. SRC-1 knockout mice also show a reduction in prostate and urethra weight compared with wild type animals. Histological examination of testes in SRC-1 null mice showed smaller glands without any apparent structural abnormalities [54].

3. The role of SRC-1 in the mammary gland

Mammary gland development is a tightly regulated, steroid dependent process. In wild type female mice, mammary gland ducts grow extensively and fill the fat pad by 8 weeks of age [60]. However, in the absence of SRC-1, ductal density is reduced and the number and extent of branching occupies much less of the fat pad area in mice of a similar age. SRC-1 is required for normal mammary duct elongation during puberty and alveolar development during pregnancy. Alveoli number and size were reduced in SRC-1 null mice compared with wild type mice of the same pregnant stage, although significantly the null mice did retain the capacity to produce milk [54].

4. The role of SRC-1 in other organs

SRC-1 is critical for appropriate brain development and function. In Purkinje cells (PCs) of the cerebellum, SRC-1 is more highly expressed than other SRC members. SRC-1 deficiency retards PC development during embryogenesis and neonatal stages. Adult SRC-1 null mice exhibit moderate motor learning deficiencies [61]. The delay of PC development at the embryonic and neonatal stages is mainly attributed to both late birth and slow migration of SRC-1 knockout PC precursors [61].

SRC-1 is a functional coactivator of the thyroid receptor (TR), and loss of SRC-1 activity causes partial resistance to thyroid hormone signaling [37, 62]. Simultaneous knockout of SRC-1 and thyroid hormone receptor proteins (SRC-1/TR α and SRC-1/TR β knockout mice) caused more significant growth retardation than single knockout of either TR β or TR α , suggesting SRC-1 is important for TR β or TR α -mediated body growth [63].

In addition, SRC-1 deletion led to skeletal resistance to estrogen predominantly in the cancellous bones [64, 65]. Under both physiological and pathological conditions, SRC-1 was shown to play an important role in the maintenance of bone mineral density by sex hormones and is necessary for protection

against osteopenia and osteoporosis [66]. Interestingly, a genetic polymorphic variant of the SRC-1 protein (SNP-12725) was found to be associated with a decrease in bone mineral density [52, 67].

Finally, SRC-1 is an important mediator of the protective effects of estrogen in the cardiovascular system. SRC-1 is expressed in the endothelial cells and the vascular smooth muscle cells (VSMCs) of the normal arterial wall. SRC-1 expression is also found in the cells of neointima, induced by vascular injury. SRC-1^{-/-} mice exhibit reduced vasoprotective capabilities in the vascular wall, which manifests as enhanced neointima formation and as a marked increase in VSMC proliferation in response to vascular injury [68]. Furthermore, SRC-1 is coexpressed with SRC-3 in the blood vessel wall and the roles of these two family members demonstrate considerable functional redundancy with regards to the execution of estrogen induced vasoprotective mechanisms [69].

5. Metabolic functions of SRC-1

The NR, PPAR γ , is critical for the development of both white and brown adipose tissue [70]. SRC-1 activity in the adipose tissue is dependent on PPAR γ and its coactivator, PPAR γ coactivator-1 (PGC-1). When PGC-1 binds to PPAR γ , it undergoes a conformational change and can complex with SRC-1 and CBP/p300, to significantly enhance the transcriptional activity of PPAR γ in brown adipose tissue [71]. Inactivation of SRC-1 impairs the thermogenic activity of PGC-1 in the brown adipose tissue, it decreases energy expenditure and increases susceptibility to obesity following a high fat diet. The ratio of SRC-1 expression relative to SRC-2 also has a significant impact on energy homeostasis as a loss of SRC-2 enables SRC-1 to bind PGC-1 with little or no competition. As a result, SRC-2^{-/-} mice have increased thermogenic activity, they are also protected against obesity and demonstrate high insulin sensitivity [72]. SRC-1 also acts in conjunction with SRC-3 to selectively regulate the expression of genes involved in brown adipose tissue development. SRC-1^{-/-}/SRC-3^{-/-} knockout mice have underdeveloped adipose tissue compartments, which are incapable of lipid storage and consequentially, demonstrate defective thermogenic response mechanisms [73].

Finally, in the liver, SRC-1 controls hepatic glucose production via its coactivation of the non steroidal C/EBP α transcription factor. C/EBP α signals through a feed-forward loop to transactivate pyruvate carboxylase, which is a crucial gene for the initiation of gluconeogenesis. SRC-1 null mice are hypoglycemic in both fed and fasting states, it is thus suggested that C/EBP α is unable to function in the absence of

SRC-1. Hence, SRC-1 has a key role in the maintenance of glucose homeostasis in the liver [74]. SRC-1 also functions in the liver to coactivate the LXR α /RXR heterodimer. LXR α is commonly involved in lipid homeostasis and fatty acid synthesis in the hepatocytes. In this context, SRC-1 signals in conjunction with the LXR α /RXR heterodimer to upregulate transcription of the ABC transporter protein, ABCA1, which accelerates fecal cholesterol disposal by decreasing the efficiency of cholesterol absorption. DAX-1 is a member of the nuclear receptor superfamily that can repress other NR-mediated transcription. In the liver, DAX-1 directly interacts and competes with SRC-1 to repress LXR α transcriptional activity in the liver and control lipid homeostasis [75]. The ability of coactivators to compete and synergistically regulate transcription in response to homeostatic signals is an important aspect of their basic biological functions.

6. Redundant functions with other SRC proteins

Given the structural homology of the p160 family members, it is expected that SRC-1 would have certain redundant functions with SRC-2 and SRC-3 [76]. Genetic studies in mice have demonstrated partial functional redundancy between SRC-1 and SRC-2 with regards to postnatal survival and growth [77]. Furthermore, analysis of SRC-2 ablation in the testes results in abnormal spermatogenesis, age-dependent degeneration of seminiferous epithelium, and disorder of cholesterol homeostasis. However, this phenotype is significantly worsened in SRC-2 null mice with heterozygous SRC-1 knockout [77].

Further compensatory action was observed in the uterus of PR^{Cre/+};SRC-2^{flox/flox} mouse, where the additional loss of SRC-1 resulted in the complete absence of a decidual response. This indicates that the co-expressed SRC-2 and SRC-1 in the uterus cooperate in progesterone-initiated transcriptional programs to coordinate decidualization [78].

It was discovered that SRC-1 and SRC-3 both function to support labyrinth morphogenesis of the placenta. The labyrinth is an important component of the placenta which connects the maternal blood sinuses and fetal vascular networks. A double knockout of SRC-1 and SRC-3 increased proliferation of labyrinth trophoblasts and progenitor gene expression whilst down-regulating the expression of differentiation-related genes. Deficiency of SRC-1 and SRC-3 also affected the expression of several genes relevant to placental morphogenesis and glucose transportation. It was also noted that labyrinths of SRC-1/SRC-3

knockout embryos were smaller than wild type and single knockout embryos [79].

SRC-1 can also cooperate with SRC-3 to enable embryo survival. The majority of SRC-1 and SRC-3 double-knockout embryos die by E13.5. In contrast, SRC-1 single knockout embryos develop normally and SRC-3 single knockout embryos only exhibit partial lethality [79].

The Role of SRC-1 in Breast Cancer

SRCs are expressed at low levels in multiple tissues fundamental to the proper growth and development of these organs and SRCs often contribute to cancer in the same tissues. The general consensus as reported from both molecular and clinical studies of breast cancer is that SRC-1 has specific roles in the

mediation of metastasis, in the switch from steroid dependent to steroid independent regulation and in the prediction of disease recurrence.

1. SRC-1 expression in human breast tumors

SRC-1 protein expression is very low in human mammary gland ductal epithelial cells although it is steadily detectable in the nuclei of mouse mammary ductal epithelial cells. However, SRC-1 protein was detected in 19% to 34% of human breast tumors. SRC-1 expression is significantly associated with large, high grade tumors, HER2 positivity, disease recurrence and resistance to endocrine therapy. SRC-1 expression also serves as an independent predictor of disease-free survival (Table 1) [14, 80, 81].

Table 1. IHC Analysis of SRC-1 Protein Expression in Human Breast Cancer.

References	SRC-1 Expression by IHC, (n)	Molecular Association	Pathological Association	Additional Observations
Hudelist et al. 2003	28% (25)	ER β +, SRC-2+	No association between SRC-1 and normal or malignant cancer	-
Fleming et al. 2004a	29% (52)	ER α +	Poor outcome Lymph node positive patients	92% of recurrences were SRC-1 positive SRC-1 associated with resistance to endocrine therapy
Fleming et al. 2004b	26% (70)	HER2+ PEA3+	Reduced disease free survival Recurrence	Significant predictor of time to disease recurrence
Myers et al. 2004	19% (150)	HER2+ ER β -	Larger tumors (>35mm) Reduced disease free survival	90% of recurrences were SRC-1 positive Significant predictor of disease free survival
Myers et al. 2005	24% (134)	HER2+ Ets-1+ Ets-2+	High grade tumors Recurrence	Both Ets-1 and Ets-2 colocalize with SRC-1 in tumor cells SRC-1 associates with phospho-Raf
Redmond et al. 2009		HER2+ COX2+		Significant predictor of time to disease recurrence Increased SRC-1 colocalization with ER α in Tamoxifen-treated recurrences
McIlroy et al. 2010	34% (560)	HOXC11+ S100 β +	Distant metastasis Reduced disease free survival	SRC-1 and HOXC11 are strong predictors of reduced disease free survival in a Tamoxifen treated population
McCartan et al. 2011		ADAM22+		SRC-1 and ADAM22 are independent predictors of disease recurrence

IHC immunohistochemistry; n, number of patient population; (+), positive association; (-), negative association; ER, estrogen receptor.

2. The SRC-1^{-/-};MMTV-PyMT model

The role of SRC-1 in mammary tumor initiation, progression and metastasis has been investigated by knocking out SRC-1 in the *MMTV-PyMT* (mouse mammary tumor virus-polyoma middle T) transgenic mice [82]. Analysis of mammary tumorigenesis in *SRC-1^{-/-};MMTV-PyMT* and *MMTV-PyMT* mice revealed that SRC-1 is not required for mammary tumor initiation and growth. However, SRC-1 does impact on the differentiation and polarized structuring of the mammary epithelial tumor cells in the three-dimensional culture [82]. Furthermore, SRC-1

activity has been strongly associated with mammary tumor cell intravasation and metastasis to the lungs. Blood samples taken from *MMTV-PyMT* mice showed a significantly higher number of mammary tumor cells in the circulation than that from the *SRC-1^{-/-};MMTV-PyMT* mice, indicating that SRC-1 promotes migration of breast cancer cells and invasion of these tumor cells into the vascular system.

SRC-1 expressed in the mammary tumor cells also upregulates the expression and secretion of colony stimulating factor-1 (CSF-1) to facilitate the recruitment of macrophages to the mammary tumor sites [82]. Macrophage recruitment has been associ-

ated with invasiveness and metastasis of breast tumor cells to local and distant sites [83]. At the tumor site, macrophages secrete factors such as EGF and TGF- β 1 that stimulate proliferation and invasiveness of tumor cells [84]. Macrophages also induce angiogenesis via secretion of proangiogenic cytokines such as TNF- α and IL-8. In turn, these stimulate c-Jun-NH₂-kinase and NF κ B signaling pathway to induce local release of the proinvasive angiogenesis-inducing MMP enzymes.

Importantly, the metastatic nature of SRC-1 is intrinsic to the tumor cells as demonstrated by reciprocal transplantation of *MMTV-PyMT* and *SRC-1^{-/-};MMTV-PyMT* tumors into *SRC-1^{-/-}* and wild type recipient mice [82]. In the *MMTV-PyMT* model, loss of SRC-1 also correlated closely with reduced expression of the HER2 oncogene as well as with reduced levels of the steroid independent transcription factor Ets2, thus further confirming the associations between SRC-1 and growth factor signaling effectors in breast cancer [82].

3. The SRC-1;MMTV-neu model

The *SRC-1^{-/-};MMTV-neu* mouse breast cancer model was generated by crossing *MMTV-neu* transgenic mice with *SRC-1* knockout mice. In this model, SRC-1 deficiency increased tumor latency and reduced tumor cell proliferation index and lung metastasis. As observed in the *SRC-1^{-/-};MMTV-PyMT* model, *SRC-1^{-/-};MMTV-neu* tumors were also more differentiated than the *MMTV-neu* tumors. Molecular analysis demonstrated an increase in the expression of several cell cycle inhibitors [85].

The findings from both *SRC-1^{-/-};MMTV-PyMT* and *SRC-1^{-/-};MMTV-neu* breast cancer models indicate that SRC-1 plays a crucial role in promotion of breast cancer metastasis, while in the *MMTV-neu* model SRC-1 also enhances tumor initiation and growth, suggesting that the role of SRC-1 on tumor growth may be specific to individual oncogene-induced tumorigenic pathways. In addition, since the tumors from both models are ER negative, SRC-1 likely promotes tumorigenesis and metastasis in these models through estrogen-independent pathways.

4. Growth factor signaling and SRC-1

SRC-1 is highly expressed in HER2 positive breast cancers [80, 81, 86] and has been shown to co-activate Ets2, a transcription factor activated by the HER2-MAPK signaling pathway. Under the influence of HER2, Ets2 and SRC-1 are recruited to the promoter of the *c-myc* oncogene. In turn, c-myc expression promotes breast tumor cell survival, metastasis and

resistance to both Tamoxifen and aromatase inhibitors [87, 88].

Simultaneous overexpression of SRC-1 and HER2 frequently occurs and has important implications in tumor cell proliferation. SRC-1 mediates overexpression of stromal cell-derived factor alpha (SDF-1 α) while HER2 signaling mechanisms mediate the stabilization of SDF-1 α 's specific receptor CXCR4 [89]. It has been reported that SDF-1 α :CXCR4 signaling complex is required for the proliferation of cancer cells at sites of metastasis [90]. The formation of the SDF-1 α :CXCR4 complex is one example of the ability of SRC-1 signaling to crosstalk with that of other pathways and therein promote disease progression.

5. Mechanisms of SRC-1 action in breast cancer metastasis

A role for SRC-1 in breast cancer metastasis has been established and to date, two distinct mechanisms have been elucidated. In the first instance, SRC-1 impacts on the epithelial to mesenchymal transition (EMT) and epithelial depolarization via regulation of the EMT transcription factor Twist. In the second, SRC-1 upregulates the expression of integrin α ₅ to promote cell migration and invasion.

Twist: EMT is characterized by the loss of epithelial differentiation and the gain of mesenchymal properties within the cellular population. This transition enables tumor cells to invade and survive in the stromal tissues. In essence, EMT may be an early step towards metastasis and is characterized by certain gene expression changes [17, 91]. *In vitro* experiments from the wild type and SRC-1 knockout cell lines show that SRC-1 inversely correlates with the major EMT hallmark protein, E-cadherin. Furthermore, SRC-1 regulates the EMT transcription factor, Twist, a known suppressor of E-cadherin. It serves as a master molecular switch of the EMT program [92].

Observations from HER2-positive cancer cells suggest that the MAPK pathway controls the direct phosphorylation, stabilization and accumulation of Twist protein expression. This was further confirmed in tumor samples where HER2 positively correlated with Twist phosphorylation, total Twist protein expression and activity of the c-Jun N-terminal kinase (JNK). JNK is a member of the MAPK family. Moreover, Twist is a transcriptional target for SRC-1 and the polyoma enhancer activator 3 (PEA3), a downstream MAPK effector [17]. Incidentally, these observations in HER2 positive tumors also correlate with negative PR status and are independent of ER α status. PR negative cancers are more aggressive and have associations with resistance to therapy and bone me-

tastasis hence substantiating the tumorigenic potential role of Twist in breast cancer [93].

Integrin α_5 : SRC-1 can also mediate metastatic action in conjunction with the non-steroidal transcription factor AP-1 and the tumor microenvironment. Resident fibroblasts produce abundant extracellular matrix (ECM) proteins to provide anchorage for tumor cell adhesion and migration [94]. Heterodimeric integrin transmembrane receptors bind to ECM proteins to transport signals bidirectionally across the cell membrane, allowing cells to respond to environmental changes [94]. In breast cancer, these integrin receptors have been associated with tumor cell survival, growth and metastasis in an anchorage-independent manner. In particular, the heterodimeric receptor, $\alpha_5\beta_1$, is increased in malignant breast cancer and is associated with poor prognosis [95]. SRC-1 serves as a coactivator for the transcription factor AP-1, the two complexing together at the promoter of the integrin α_5 gene, enhances its transcription. In the absence of SRC-1 cell adhesion and migration via the ECM-integrin-focal adhesion kinase (FAK) pathway are reduced. The downstream signaling components of this pathway are also significantly reduced in the absence of SRC-1 and the integrin α_5 [16], suggesting that integrin α_5 is a key target gene of SRC-1 in its efforts to orchestrate the local invasion and metastatic survival of breast cancer tumor cells.

6. SRC-1 and resistance to Tamoxifen therapy

SRC-1 has been increasingly cited with regards to the development of resistance to endocrine therapy in breast cancer. Resistance to endocrine therapy represents a serious clinical dilemma and is an increasingly prevalent occurrence among breast cancer patients. Tamoxifen is a selective estrogen receptor modulator (SERM) and is the most common anti-estrogen therapy prescribed for pre-menopausal ER α -positive breast cancers. Studies carried out in HeLa cells where Tamoxifen is an agonist, have shown that overexpression of SRC-1 further increases the activity of Tamoxifen [96]. Similarly, in the Ishikawa endometrial cancer cell line where Tamoxifen is also agonistic, high levels of SRC-1 expression were reported compared to the MCF-7 breast cancer cell line [97]. Interestingly, src kinase activity has been shown to specifically enhance SRC-1 and CBP activity in these Ishikawa cells [48], thus associating high levels of SRC-1 protein and growth factor signaling pathways with tissues that are receptive to the agonistic properties of Tamoxifen [97]. In addition, a non-synonymous small nucleotide polymorphism (SNP-P1272S) was identified in the DNA sequence of

SRC-1, which decreased SRC-1 activity. Specifically, this study also demonstrated that the SNP-P1272S had a negative impact on the agonistic effects of Tamoxifen on bone mineral density in post menopausal women [52].

With regards to the development of resistance, it was reported that SRC-1 overexpression could convert Tamoxifen from a transcriptional repressor to a transcriptional activator in breast cancer [98]. It has been shown that SRC-3 could compete with the Tamoxifen-recruited transcriptional repressor PAX and result in upregulation of HER2 expression [99]. The stoichiometry of PAX and SRC-3 was thus shown to dictate the efficacy of Tamoxifen treatment in breast cancer as HER2 and SRC-3 upregulation have been positively associated with the development of Tamoxifen resistance in breast cancer. Similar effects have also been seen with NRs other than ER, as overexpression of SRC-1 is also capable of inducing PR activity in the presence of the PR antagonist RU486 [100].

As therapeutic resistance becomes more prevalent, the ability to predict positive patient response to Tamoxifen is becoming increasingly important. Treatment with Tamoxifen itself has been shown to increase the expression levels of both SRC-1 and SRC-3 in multiple studies [101, 102]. It was observed that the expression of SRC-1, SRC-3 and multiple cell cycle and cell adhesion genes was increased, while the expression of apoptotic genes and PR was concomitantly downregulated during the development of a Tamoxifen-resistant cell line. Loss of PR is indicative of an alteration in tumor steroid receptor profile, which is a common feature in the development of Tamoxifen resistance. Interestingly, the SRC-1 protein level was decreased in the resistant cells once Tamoxifen treatment was stopped for a 12 months period [103]. It was also reported that the co-association of SRC-1 and SRC-3 with ER α was increased in LY2 endocrine-resistant breast cancer cells following Tamoxifen treatment in comparison with endocrine-sensitive MCF-7 cells, and that the colocalization of SRC-1 and SRC-3 with ER α was significantly enhanced in patients who have relapsed on endocrine treatment in comparison with those patients who did not undergo recurrence. Overall, analysis of the clinical data suggest that SRC-1 is a strong independent predictor of reduced disease free survival and that the interactions of the p160 SRC proteins with ER α can predict the response of patients to endocrine therapy [104].

An aberrant up-regulation of growth factor pathways which target the activity of SRC proteins is a common feature in the development of an endocrine

resistant phenotype. The HER2 pathway induces protein kinase A (PKA) to phosphorylate ER α at serine 305 in the presence of Tamoxifen. This phosphorylation alters the orientation of ER α and SRC-1 and switches Tamoxifen to an ER α agonist, resulting in RNA Polymerase II recruitment and transcriptional initiation [105]. These findings were supported by a separate study in which Tamoxifen resistance was also associated with ER α phosphorylation at serine 305 [106].

Additional clinical data showed an increased co-association of SRC-1 with MAPK-activated transcription factors PEA3 and Ets2 in a Tamoxifen treated patient population [14, 86]. As expected, both of these co-associations correlated positively with HER2 positivity in the same population. In agreement with the upregulation of c-myc by Ets2 and SRC-1 in cultured cells, this upregulation was also observed in the Tamoxifen-treated patient population.

More recent data has identified two more transcription factors that work with SRC-1. Firstly, HOXC11, a member of the homeobox family of developmental proteins was identified as a functional binding partner for SRC-1 in Tamoxifen-resistant LY2 cells. Hox family proteins have been implicated in EGF-mediated migration and adhesion as well with the agonistic properties of Tamoxifen. Immunohistochemical analysis of a Tamoxifen-treated patient population showed increased localization and expression of HOXC11 in the nuclei of tumor cells. Strong associations were also observed between HOXC11 and SRC-1 in the resistant LY2 cells compared to the Tamoxifen-sensitive MCF-7 cells. This observation was repeated in the patient population. Moreover, coexpression of HOXC11 with SRC-1 was noted as a superior predictor of poor clinical prognosis than any of the other classic parameters [15]. This study also recognized S100 β as the transcriptional target for the HOXC11 and SRC-1 complex. In breast cancer patients, the elevated levels of S100 β significantly predicted poor disease free survival. Since S100 β is detectable in human serum, it can be potentially used as a biomarker to predict and monitor disease progression.

Secondly, SRC-1 interacts with the transcription factor MYB to directly regulate ADAM22, a non-protease member of the ADAM family of disintegrins [107]. Molecular analysis carried out in Tamoxifen-resistant cell lines discovered a role for ADAM22 in cellular migration and differentiation. In addition, expression of ADAM22 mRNA was increased in the Tamoxifen-resistant tumors in xenograft mouse models. Furthermore, ADAM22 expression was identified by immunohistochemical analysis

in a clinical patient population as an independent predictor of poor disease free survival [107]. ADAM22 has also been proposed as a potential therapeutic target as its migratory action can be inhibited following treatment with its ligand LGI1 [107].

7. SRC-1 and resistance to aromatase inhibitor therapy

SRC-1 activity has been found to be associated with resistance to aromatase inhibitors (AIs). Like Tamoxifen resistance, AI resistance is also marked by a shift in cancer cell signaling from steroid dependency towards dependency on peptide growth factors. In AI resistant cell lines, loss of SRC-1 improved cells' ability to differentiate while reducing their migratory capacity. Interestingly, loss of ER α in these cells failed to impact on migration. This indicates that SRC-1 may also act in a steroid independent manner to promote AI resistance. In AI-resistant cells, SRC-1 also interacts with MAPK-activated Ets2 transcription factor. Specifically, SRC-1 and Ets2 are recruited to the c-myc and MMP9 promoters upon AI (Letrozole) treatment. Importantly, in an AI-treated patient population with two thirds of SRC-1-positive and one third of SRC-1-negative primary tumors, all AI-treated patients with disease relapse from original SRC-1-negative tumors presented AI-resistant SRC-1-positive tumors. This finding has important and exciting implications for the specific ability of SRC-1 to advance metastasis in AI-treated breast cancer [88].

SRC-1 in Prostate Cancer

SRC-1 has been linked to prostate cancer and extensively evaluated as an AR coactivator in both androgen-dependent and independent disease. In localized, androgen-dependent tumors, increased SRC-1 expression correlates with lymph node metastasis [108]. Ablation of SRC-1 in androgen-dependent LNCaP prostate cancer cells represses activation of AR target genes and reduces AR-dependent cellular proliferation [108]. Furthermore, in CV1 cells, SRC-1 overexpression increases the androstenedione-induced AR activity [109].

SRC-1 also has a role in androgen-independent prostate cancer. Although one clinical study found SRC-1 mRNA expression was lower in therapy-resistant prostate cancer compared with untreated patients [110], others evaluating tumors from resistant patients found SRC-1 expression significantly increased in hormone-refractory tumors compared to androgen-dependent tumors or benign prostatic hyperplasia [109, 111]. Re-activation of AR-mediated transcriptional programs in the absence of androgen

is critical for the growth and survival of the majority of castration-resistant tumors. The elevated expression of SRC-1 in these prostate tumors raises a possibility that SRC-1 may support androgen-independent and AR-mediated transcription and promote hormone-refractory tumor growth. In support of this idea, CWR22 human prostate cancer cells xenografted into mice have decreased SRC-1 expression immediately following castration, but have significantly increased SRC-1 expression at the time of tumor relapse [109]. In androgen-independent C4-2 prostate cancer cells that depend on AR for proliferation, knockdown of SRC-1 significantly reduced growth and AR target gene expression. In contrast, knockdown of SRC-1 had no effect on the growth of the AR-negative PC-3 and DU145 prostate cancer cell lines [108]. Finally, SRC-1 is involved in ligand-independent activation of AR by IL-6, a cytokine that regulates proliferation, apoptosis and angiogenesis in prostate cancer [112].

The direct *in vivo* contribution of SRC-1 to prostate cancer was investigated through the use of genetically engineered mouse models. The SRC-1 gene was deleted in TRAMP mice, which harbor the oncogenic SV40 T/t antigen transgene driven by the prostate epithelium-specific probasin promoter [113]. Tumor mass, histology and biomarkers in cancers from these mice were assessed at various ages; however no significant difference in tumor initiation or progression between SRC1^{-/-} and wild type TRAMP mice was found. Interestingly, expression of SRC-3, was significantly elevated thus indicating that, in TRAMP mice, SRC-1 and SRC-3 may have analogous functions and SRC-3 over-expression may be able to compensate for SRC-1 deficiency [113]. Although its contribution to tumorigenesis is non-essential in TRAMP mice, the significant findings in human samples and cell lines suggest that SRC-1 may still be a critical prostate cancer mediator.

SRC-1 Expression in Other Cancers

I. Endometrial cancer

SRC-1 dysregulation has been reported in endometrial cancer. SRC-1 mRNA levels are significantly increased in malignant endometrial cancer and the high expression of SRC-1 positively correlates with ER α and PR expression. However, no significant correlation was found between SRC-1 mRNA expression and grade, stage, or depth of myometrial invasion [114]. Conversely, SRC-1 expression was reported as reduced in the less aggressive endometrial hyperplasia and in endometrial carcinoma compared with normal glandular cells in the proliferative phase [115].

2. Thyroid cancer

In thyroid cancer, SRC-1 is expressed in epithelial tumor cells. In non-anaplastic tumors, SRC-1 expression is significantly associated with HER2 expression, and together their levels correlate with poor cellular differentiation, capsular invasion and disease progression. In anaplastic thyroid tumors, SRC-1 is expressed in 87% of samples and again positively correlates with reduced survival rate ($p < 0.001$) [116].

3. Cutaneous melanoma

Analogous to that observed in breast cancer, SRC-1 also serves as a coactivator for HOXC11 to up-regulate S100 β in cutaneous melanomas. Serum levels of S100 β have been proposed as a marker of tumor burden, predicted poor response to treatment and poor prognosis in melanoma patients [117, 118]. Higher expression levels and co-association of SRC-1 and HOXC11 were reported in malignant melanoma compared to benign nevi. The same was also observed in a metastatic melanoma cell line. Interestingly, disruption of HOXC11 and SRC-1-regulated S100 β in malignant cells using the dual Src/Abl inhibitor, Dasatinib, can interfere with the phosphorylation of SRC-1 by Src kinase [119]. This may represent a new therapeutic approach for the treatment of advanced melanoma.

SRC Proteins as Potential Therapeutic Targets

Given the wide-reaching oncogenic effects of the SRC proteins, particularly SRC-1 and SRC-3, significant strides are being made to elucidate their potential as effective biological therapeutic targets. Previous reluctance to pursue SRCs as therapeutic targets arose from their large size, lack of structural conformity and the absence of any high affinity ligand-binding domains. However, new proof of principle experiments has challenged this view and shown that small molecule inhibitors (SMIs) such as gossypol, a natural polyphenol, are capable of reducing SRC-1 and SRC-3 proteins in MCF-7 and other cancer cell lines. Interestingly, SRC-2 was not susceptible to the inhibitory effects of gossypol treatment. Gossypol was shown to physically interfere with the binding between the SRC-3 RID and the ER α ligand binding domain. However, the resultant degradation of SRC-1 and SRC-3 occurred independently of a proteasomal mechanism. This ability of gossypol to reduce SRC-1 and SRC-3 proteins was also maintained independently of the various ER ligands such as estrogen, Tamoxifen and ICI 182,780. Moreover, the gossypol action is independent of ER α as it also degrades

SRC-3 in ER α negative cancer cells. Treatment of cancer cells with gossypol also resensitized the cells to MEK, EGF and IGF pathway inhibitors. Of significant importance, this form of SMI treatment is preferentially toxic to cancerous cells and is relatively selective

for SRC-1 and SRC-3 [120]. This work is the first to show that SRC proteins are accessible to SMI-based chemotherapy. Continued research into this area could have significant implications for treatment of cancers, especially those resistant to current therapies.

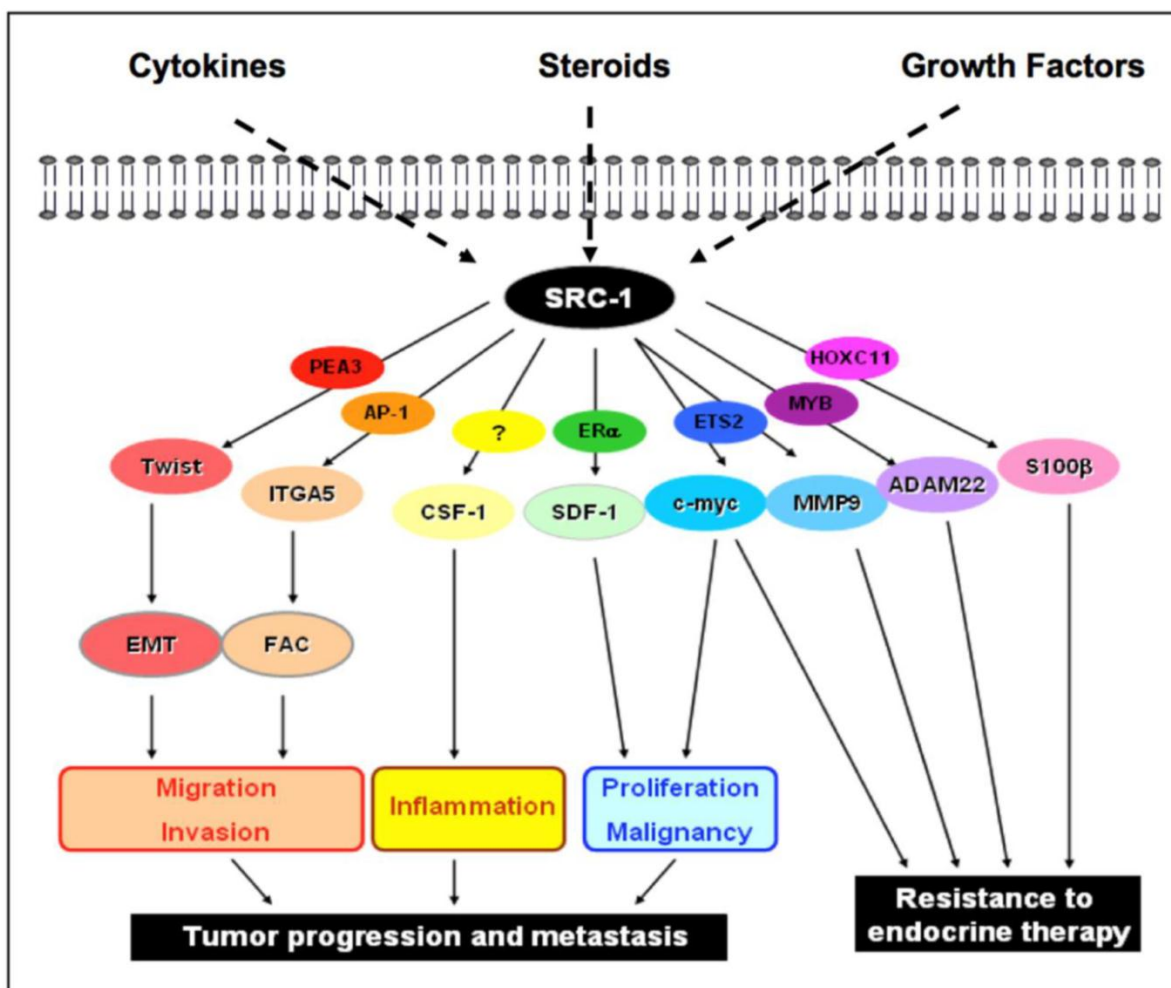


Figure 3. SRC-1 coregulator activity in breast cancer. SRC-1 is susceptible to activation by the cytokine, steroid or growth factor pathways. These pathways encode the SRC -1 protein to coactivate a specific transcription factor in order to mediate specific transcriptional events within the nucleus. The schematic diagram illustrates the potential transcriptional binding partners of SRC-1 and their respective downstream effector targets. Under the influence of either steroid dependent or steroid independent signaling networks, SRC-1 will interact with different transcription factors to form varying complexes for transcriptional regulation of tumor cell processes that will promote an increasingly aggressive and resistant tumor phenotype. EMT: epithelial mesenchymal transition; FAC: focal adhesion complex.

Conclusion

The discovery and characterization of the p160 SRC family have revolutionized the field of molecular endocrinology and endocrine-related oncology. SRCs have been described as “the powerhouses of transcription” and have been rightfully reclassified as “master genes” on the basis of their ability to bind across unrelated families of transcription factors and

coordinate the regulation of multiple genes in multiple complex physiological states [121]. SRC-1 epitomizes all of these master qualities and the recent work outlined in this review highlights this transcriptional coactivator as a key player in normal development, multiple cellular signaling crosstalk, promoting resistance to endocrine treatments and coordination of tumor cell metastasis.

Acknowledgements

This work is partially supported by Cancer Prevention and Research Institute of Texas grant RP101251-P4 and National Institutes of Health grants R01 CA112403 and R01 DK058242 to J.X., Department of Defense Prostate Cancer Research Program Pre-doctoral Scholarship PC102004 to J.C.Y.T., and grants from Science Foundation Ireland (B1853) and Health Research Board, Ireland (PHD/2007/11) to L.S.Y. and C.A.W.

Conflict of Interests

The authors have declared that no conflict of interest exists.

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